THE EFFECT OF SMOKING STATUS ON THE EFFICACY OF THE SMART REGIMEN IN HIGH RISK ASTHMA

[1,2 *]Janine Pilcher, BSc, MBChB, [1,2,3 *]Mitesh Patel, BMedSci, BMBS, MRCP, PhD,

[4]Helen K Reddel, MBBS, PhD

[1]Alison Pritchard, [5]Peter Black MBChB, FRACP (deceased), [3]Dominick Shaw MD, FRCP,

[6]Shaun Holt, MBChB,

[2,7]Mark Weatherall, MBChB, FRACP, [1,2]Richard Beasley, MBChB, DSc,

[1]Medical Research Institute of New Zealand, Wellington, New Zealand
[2]Capital & Coast District Health Board, Wellington, New Zealand
[3]Nottingham Respiratory Research Unit, School of Medicine, University of Nottingham, United Kingdom
[4]Clinical Management Group, Woolcock Institute of Medical Research, University of Sydney, Australia
[5]University of Auckland, Auckland, New Zealand
[6] Clinicanz, Tauranga, New Zealand
[7]University of Otago, Wellington, New Zealand

Word count: 2,565 (abstract 223)

*JP and MP are joint first authors

Correspondence:

Janine Pilcher

Medical Research Institute of New Zealand

Level G, CSB Building, Wellington Hospital,

Private Bag 7902, Wellington 6242, New Zealand

Telephone: 64-4-805 0241, Fax: 64-4-389 5707

Email: janine.pilcher@mrinz.ac.nz

SUMMARY AT A GLANCE (32 words)

This study has shown that the favourable efficacy/safety profile of single combination ICS/LABA inhaler maintenance and reliever therapy regimen in adult patients with high risk asthma is not influenced by smoking status.

ABSTRACT (223 words**)**

Background and objective: The optimal management of people with asthma with a significant smoking history is uncertain. The aim of this study was to determine whether the efficacy/safety profile of single combination inhaled corticosteroid/long acting beta-agonist inhaler maintenance and reliever therapy is influenced by smoking status.

Methods: We undertook secondary analyses from an open-label 24-week randomised study of 303 high risk adult asthma patients randomised to budesonide/formoterol 200-6µg metered dose inhaler for maintenance (2 actuations twice daily) and either budesonide/formoterol 200-6µg metered dose inhaler 1 actuation ("SMART" regimen) or salbutamol 100µg 1-2 actuations for symptom relief ("Standard" regimen). Smoking status was classified in to three groups; as "current", "ex" or "never" and a smoking/treatment interaction term tested for each outcome variable. The primary outcome variable was number of participants with at least one severe exacerbation.

Results: There were 59 current, 97 ex and 147 never smokers included in the analyses. The smoking status/treatment interaction term was not statistically significant for any of the outcome measures. With adjustment for smoking status, the number of participants with severe exacerbations was lower with the SMART regimen (OR 0.45, 95% CI 0.26-0.77, P= 0.004; P value for interaction between smoking status and treatment 0.29).

Conclusions: We conclude that the favourable safety/efficacy profile of the SMART regimen applies to patients with high risk asthma, irrespective of smoking status.

KEY WORDS

Adult

Asthma

Medication adherence

Randomised controlled trial

Smoking

SHORT TITLE

Smoking status and the SMART regimen

ABBREVIATIONS

ACQ: Asthma control questionnaire

COPD: Chronic obstructive pulmonary disease

ED: Emergency Department

FEV_1: forced expiratory volume in 1 second

ICS: Inhaled corticosteroid

LABA: Long acting beta-agonist

MDI: Metered dose inhaler

RCT: Randomised controlled trial

SABA: Short acting beta- agonist

SMART: Single maintenance and reliever therapy

INTRODUCTION

The management of individuals with asthma who smoke is an important clinical priority.[1,2] Cigarette smoking is associated with greater morbidity from asthma and a higher risk of severe exacerbations.[3-5] Amongst individuals with asthma, heavy smokers are at greater risk of asthma mortality compared with non smokers.[6] The optimal management of asthmatics who smoke is uncertain. Large randomised controlled trials (RCTs) that inform asthma management guidelines generally exclude current smokers or ex smokers with at least a 10 year pack year history to avoid recruitment of patients with concomitant chronic obstructive pulmonary disease (COPD).[7] Furthermore it is known that individuals with asthma who smoke benefit less from inhaled corticosteroid (ICS) and oral corticosteroid therapy in terms of symptoms, lung function, and risk of severe exacerbations.[8-13]

In patients with severe asthma the use of a single combination ICS/fast-acting long-acting beta-agonist (LABA) inhaler as both maintenance and reliever therapy, (the SMART regimen), leads to reduced risk of severe exacerbations compared with combination ICS/LABA inhaler as maintenance and short-acting beta-agonist (SABA) for reliever therapy.[14-16] This is based on RCTs that did not report treatment effects in relation to smoking status.[14-16] It is therefore uncertain if the favourable efficacy/safety profile of the SMART regimen can be generalised to patients with severe asthma who have important current or ex smoking histories. The SMART regimen could have a greater relative benefit for smokers with asthma because the increased ICS dose may partially reverse the reduced ICS responsiveness.[10]

Alternatively, the SMART regimen may be less beneficial for smokers with asthma because of lesser efficacy from the increased use of ICS during worsening symptomatic asthma. Smokers with asthma may also have different responses to variable dosing of LABA and SABA therapy, compared to non smokers.

In recognition of the potential role for smoking status in response to treatment, this study reports a secondary analysis investigating whether smoking affects the efficacy of the SMART regimen in a RCT of high risk adults with asthma, of whom 51% were current or ex smokers.[17] Our hypothesis was that current and ex smokers would have worse clinical outcomes than non smokers and lesser efficacy from the SMART regimen compared with non smokers.

METHODS

Design

This multicentre open-label study randomised 303 asthma patients to the SMART or the Standard therapy regimen.[17] The study was approved by the New Zealand Multi-Region Ethics Committee and has the Australian and New Zealand Clinical Trials Registry number ACTRN12610000515099. Full written informed consent was required prior to study participation.

Participants

Participants were aged 16 to 65 years and had a current prescription for ICS with at least one asthma exacerbation (presentation to an Emergency Department (ED) or general practice resulting in a prescription for oral corticosteroids or treatment with spacer-delivered or nebulised bronchodilator, or self-administration of prednisone for asthma for at least 3 days) in the previous year.[17] Exclusion criteria included a diagnosis of COPD or onset of respiratory symptoms after the age of 40 in current or ex smokers with a ≥10 pack year smoking history. The study protocol is available at http://www.mrinz.ac.nz/uploads/mrinz/SMART_Protocol.pdf.

Interventions

Participants were randomised 1:1 to receive either the SMART regimen, which was 200/6 micrograms (mcg) budesonide/formoterol via metered dose inhaler (MDI) (Vannair, AstraZeneca Limited, Auckland, New Zealand; this is the MDI formulation of Symbicort Turbuhaler) for maintenance (two actuations twice daily) and one actuation as required for symptom relief, or the Standard regimen consisting 200/6mcg budesonide/formoterol via MDI for maintenance (two actuations twice

daily) and 100mcg salbutamol via MDI (Ventolin, GlaxoSmithKline Limited, Auckland, New Zealand), 1-2 actuations as required for symptom relief. At the first visit participants were given a written asthma self-management plans and inhaler technique was checked. Subsequent visits took place at weeks 3, 10, 17, and 24.

The Smartinhaler Tracker (Nexus6 Limited, Auckland, New Zealand) electronic monitor was incorporated into all MDIs, and recorded the date and time of each actuation. Detailed trial quality control processes took place.[18,19] Data were uploaded from the inhalers at each visit.

Data analysis and study outcomes

Data analysis was by intention to treat.

The primary outcome variable was the number of participants with at least one severe exacerbation, according to the ATS/ERS Taskforce criteria: the use of systemic corticosteroids for at least 3 days, or admission to hospital or visit to the ED because of asthma that required systemic corticosteroids.[20] High beta-agonist use was defined as >16 actuations of salbutamol in the Standard regimen and >12 actuations of budesonide-formoterol for the SMART regimen (i.e. > eight actuations of budesonide/formoterol, additional to the four maintenance doses), in 24 hours. These definitions were based on self-management plan recommendations for beta-agonist use requiring medical review,[21, 22] and supported by the bronchodilator equivalence of 6mcg formoterol to 200mcg salbutamol with repeat dosing in acute asthma.[23, 24] For the Standard regimen, marked and extreme beta-agonist overuse

were defined as >24 and >32 salbutamol actuations in 24 hours, respectively. For the SMART regimen, marked and extreme overuse were defined as >16 and >20 budesonide-formoterol actuations in 24 hours, respectively (i.e. >12 and >16 actuations of budesonide/formoterol, additional to the four maintenance doses, respectively).

Odds ratios for the risk of at least one severe exacerbation by randomised group, the primary outcome variable for this analysis, were estimated by logistic regression. Secondary outcome variables analysed by logistic regression were: at least one hospital or ED attendance; at least one day of: beta-agonist overuse, marked overuse, or extreme overuse; one or less budesonide/formoterol inhaler actuations per day; or no budesonide/formoterol inhaler actuations per day over the study period. Relative rates by Poisson regression, with an offset for the observation time, were used for the count variables including number of severe exacerbations and number of courses of oral corticosteroids; and number of days of high use, marked overuse, or extreme overuse, or with one or less budesonide/formoterol inhaler actuations per day or no budesonide/formoterol inhaler actuations per day. ANCOVA was used for differences on the logarithm transformed scale, where exponentiation is interpreted as mean ratios, for daily equivalent ICS use. Survival analysis for day to first exacerbation used Cox Proportional Hazards. Contingency table analysis was used for oral corticosteroid dose (prednisone equivalent per year) by creating four bands of use. For this outcome the pre-specified main RCT analysis plan was to seek an appropriate transformation for the dose, such as the logarithm transformation, or use a non-parametric method (the Mann-Whitney test), to compare the groups. After the data were collected many participants were found

to have no oral prednisone use so neither of these strategies was able to be used. The other continuous variables which had appropriate data distributions were analysed by ANCOVA: Forced expiratory volume in one second (FEV_1), FEV_1 percentage predicted, Asthma control questionnaire-7 (ACQ-7).

The general analysis strategy for the secondary analysis of the effect of smoking reported here was to test a smoking-treatment interaction term for each outcome variable. Smoking was classified as: “current smoker”, “ex smoker”, and “never smoker”. Participants reported which category they belonged to at the first study visit. Our analysis plan was to report the difference in outcome variables between SMART and Standard for current smokers compared to never smokers, and ex smokers compared to never smokers, if there was evidence of statistical significance, $P<0.05$, for an interaction between smoking and randomised treatment. Otherwise we planned to report the difference in outcome for current smokers versus never smokers, and ex smokers versus never smokers, adjusted for randomised treatment. In this case the lack of statistical evidence of an interaction would be consistent with the same relative effect of treatment for all smoking categories.

RESULTS

Three hundred and three participants were enrolled between June 2010 and September 2011. Fifty nine (19%) were current smokers, 97 (32%) ex smokers and, 147 (49%) were never smokers (Table 1, Figure 1). Current smokers had between 0.3 and 44 pack years of smoking, and ex smokers between 0.2 and 60 pack years of smoking. Current smokers had higher ACQ-7 scores (i.e. worse asthma control) compared to ex and never smokers.

SMART versus Standard regimen, with adjustment for smoking

There was no evidence of interaction between smoking status and randomised treatment interaction term for any outcome measure. This means that the relative effect of randomised treatment was the same for participants with different smoking status (Tables 2 and 3).

The outcomes by randomised treatment, adjusted for smoking status, are shown in Tables 2 and 3. The proportion of participants with at least one severe exacerbation was lower in those randomised to the SMART regimen, with an odds ratio of 0.45 (95% CI 0.26 to 0.77), P= 0.004; P value for interaction between smoking status and treatment 0.29 (Table 2).

After adjustment for smoking status, the number of severe exacerbations was lower in participants randomised to SMART (Table 2). There was no significant difference in the composite systemic corticosteroid exposure between the two regimens following adjustment for smoking status (Table 2). In addition, the ACQ-7 scores at visit 5 were lower in the SMART group, compared with Standard (Table 2).

After adjustment for smoking status, the SMART regimen was not associated with a significantly different proportion of participants with at least one episode of high, marked or extreme beta-agonist overuse when compared to the Standard regimen (Table 3). However, the SMART group had significantly fewer number of days of high use, marked overuse, extreme overuse, and number of days of high use without medical review within 48 hours (Table 3). The number of days of non-adherence to maintenance therapy was also lower in the SMART group (Table 3).

Outcomes of smokers, ex smokers and never smokers, adjusted for treatment

After adjustment for treatment regimen, smoking status was associated with an increased risk of at least one severe exacerbation, an increased number of severe exacerbations, an increased risk of at least one hospital admission or ED attendance, an increased number of courses of oral corticosteroids, and increased composite systemic corticosteroid exposure, compared with never smokers. For each of these outcomes there was a significant difference between ex smokers and never smokers, but no significant difference between current and never smokers (Table 4).

After adjustment for treatment regimen, smoking status was associated with high, marked and extreme beta-agonist overuse, with current smokers and ex smokers having higher rates compared with never smokers (Table 5). After adjustment for treatment regimen, smoking status was associated with overuse days without medical review and the number of days of no budesonide/formoterol actuations, with more days occurring in the current smokers compared to never smokers (Table 5).

DISCUSSION

This study shows that the favourable efficacy/safety profile for the SMART regimen in high risk adults with asthma was similar regardless of smoking status. This suggests that the SMART regimen can be recommended in current and ex smokers, who represent a particularly high risk group.

The broad inclusion criteria of this RCT ensured the findings are widely generalisable to patients with high risk asthma. Fifty one percent of participants were current smokers or ex smokers, so we could robustly assess if the efficacy of the SMART regimen was influenced by smoking status. Our study complements the findings of an analysis of the influence of smoking status on response to two different maintenance dosing regimens for SMART with 200/6mcg of budesonide/formoterol, one versus two actuations twice daily.[26] In that study there was a significantly greater reduction in severe exacerbations by use of two maintenance budesonide/formoterol inhalations twice daily versus one inhalation twice daily in smokers, but not in non smokers. These findings suggested that the budesonide/formoterol maintenance dose 200/6 two puffs twice a day is the preferred maintenance dose for smokers.

Our primary outcome was the number of participants with at least one severe exacerbation, defined in accordance with the ATS/ERS Task Force criteria.[20] The SMART regimen reduced the odds of a severe exacerbation by about 50%, with adjustment for smoking status, and with no significant interaction between smoking status and randomised treatment. When adjusted for treatment regimen, smoking status had a significant effect on the number of severe exacerbations with ex smokers having a higher risk of severe exacerbations compared to never smokers. This suggests that the absolute reduction in the number of severe exacerbations with the

SMART regimen is greater in ex smokers because of their higher risk of this outcome compared with non smokers.

An important and novel feature of the RCT was the use of electronic monitors in all MDIs to capture all actuations self-administered by participants in the study.[18, 19] This builds on previous studies,[14-16] by enabling an in-depth assessment of the relative safety of the SMART regimen including measures of beta-agonist overuse, delay in seeking medical assistance in worsening asthma and systemic corticosteroid exposure. There were similar proportions with at least one episode of high, marked and extreme overuse in the two treatment groups, however the SMART regimen led to a 40-50% reduction in the number of days of high, marked and extreme overuse episodes, with no significant interaction with smoking status. We observed that current and ex smokers had a two to six-fold greater rate of these overuse episodes than never smokers, suggesting that there will be greater absolute benefit for this outcome in smokers. The SMART regimen also reduced the risk of delay in seeking medical review during worsening asthma, with no significant interaction with smoking.

The pattern of ICS use is of interest due to the reduced sensitivity to the effects of ICS therapy in smokers.[8-13] Interestingly, with electronic monitoring, we observed that current smokers were less likely to take their ICS than never smokers during the period of the study. The number of days of no ICS use was reduced with the SMART regimen, with no significant interaction between smoking status and treatment.

Overall the findings were similar to those in Māori, a disadvantaged high risk group in New Zealand with substantive morbidity from asthma,[27] in whom the relative benefits

of the SMART regimen were comparable to non-Māori.[28] Together the findings suggest that the SMART regimen may not only be preferred in a general high risk population, as recruited in this study, but also specific very high risk groups within this population such as Māori and smokers.

This analysis addresses secondary hypotheses from a RCT and thus, despite our finding of no interaction between smoking and randomised treatment, will have been at risk of Type I error rate inflation. As for most interaction analyses in RCTs the study was designed with statistical power to detect a difference in the whole group of participants. For some of the outcome variables there were low numbers of events in the smoking categories, limiting the ability to detect a moderate or weak effect of smoking status. We are confident that participants with COPD did not enter the RCT because we excluded those with an active diagnosis of COPD, and current or ex smokers who had the onset of respiratory symptoms after the age of 40 and a >10 pack year smoking history.

In conclusion the favourable efficacy/safety profile of the SMART regimen, when compared to the standard maintenance ICS/LABA and SABA reliever therapy regimen in this high risk population, also applies to current and ex smokers. Due to the higher baseline risk of morbidity and at risk behaviour in current and ex smokers, the absolute reduction in risk with the SMART regimen is greater in these patients. We recommend the use of the SMART regimen in current and ex smokers with asthma.

Acknowledgments: We are grateful to the study participants for their involvement in the study. MP is funded by a National Institute for Health Research Clinical Lectureship. The full study results have been published in The Lancet Respiratory Medicine in 2013.[17] The MRINZ is supported by Health Research Council of New Zealand Independent Research Organisation funding.

The SMART Study Group: Steering Committee: Mitesh Patel (clinical coordinating investigator), Janine Pilcher, Alison Pritchard, Kyle Perrin, Justin Travers, Dominick Shaw, Shaun Holt, Matire Harwood, Peter Black, Mark Weatherall (study biostatistician), Richard Beasley (principal investigator); **Auckland** (Henderson Medical Centre)**:** Clare McGuinness-Goodwin, Bill Mackey, Rodney Marks, Vikky Qi, Tyronne Tranquilino, Dirk Venter; **Auckland** (University of Auckland): Amy Chan; **Lower Hutt** (Tu Kotahi Māori Asthma Trust): Cheryl Davies, Ann Smith; **Sydney** (Woolcock Institute of Medical Research): Helen K Reddel; **Tauranga** (CentralMed General Practice)**:** Andrew Corin, Colin Helm, Chris Tofield; **Tauranga** (Papamoa Pines Medical Centre): Davitt Sheahan; **Wellington** (BoydHQ Limited): Craig Boyd (database engineer); **Wellington** (MRINZ): Tanya Baker, Denise Fabian, Alexander Hosking, Claire Munro, Maureen Stretch, Mathew Williams

Funding: Health Research Council of New Zealand (reference 09/108B), a government funding organisation.

Conflicts of Interests: RB has been a member of the GlaxoSmithKline (NZ), AstraZeneca and Novartis advisory boards, consulted for Cytos Biotechnology and Pharmaxis, received research grants from AstraZeneca, Cephalon, Chiesi, Genentech, GlaxoSmithKline and Novartis, payment for lectures or support to attend meetings from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Nycomed and Otsuka Pharmaceuticals.

REFERENCES

1. Polosa R, Thomson NC. Smoking and asthma: Dangerous liaisons. *Eur Respir J* 2013; **41**: 716-26.
2. Thomson NC, Chaudhuri R. Asthma in smokers: Challenges and opportunities. *Curr Opin Pulm Med* 2009; **15**: 39-45.
3. Shavit O, Swern A, Dong Q, Newcomb K, Sazonov Kocevar V, Taylor SD. Impact of smoking on asthma symptoms, healthcare resource use, and quality of life outcomes in adults with persistent asthma. *Qual Life Res* 2007; **16**: 1555-65.
4. Patel SN, Tsai CL, Boudreaux ED, Kilgannon JH, Sullivan AF, Blumenthal D, Camargo CA, Jr. Multicenter study of cigarette smoking among patients presenting to the emergency department with acute asthma. *Ann Allergy Asthma Immunol* 2009; **103**: 121-7.
5. Mitchell I, Tough SC, Semple LK, Green FH, Hessel PA. Near-fatal asthma: A population-based study of risk factors. *Chest* 2002; **121**: 1407-13.
6. Ulrik CS, Frederiksen J. Mortality and markers of risk of asthma death among 1,075 outpatients with asthma. *Chest* 1995; **108**: 10-5.
7. Travers J, Marsh S, Williams M, Weatherall M, Caldwell B, Shirtcliffe P, Aldington S, Beasley R. External validity of randomised controlled trials in asthma: to whom do the results of the trials apply? *Thorax* 2007; **62**: 219-223.
8. Chalmers GW, Macleod KJ, Little SA, Thomson LJ, McSharry CP, Thomson NC. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. *Thorax* 2002; **57**: 226-30.
9. Lazarus SC, Chinchilli VM, Rollings NJ, Boushey HA, Cherniack R, Craig TJ, Deykin A, DiMango E, Fish JE, Ford JG, Israel E, Kiley J, Kraft M, Lemanske RF, Jr., Leone FT, Martin RJ, Pesola GR, Peters SP, Sorkness CA, Szefler SJ,

Wechsler ME, Fahy JV. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. *Am J Respir Crit Care Med* 2007; **175**: 783-90.

10. Tomlinson JE, McMahon AD, Chaudhuri R, Thompson JM, Wood SF, Thomson NC. Efficacy of low and high dose inhaled corticosteroid in smokers versus non-smokers with mild asthma. *Thorax* 2005; **60**: 282-7.
11. Pedersen B, Dahl R, Karlstrom R, Peterson CG, Venge P. Eosinophil and neutrophil activity in asthma in a one-year trial with inhaled budesonide. The impact of smoking. *Am J Respir Crit Care Med* 1996; **153**: 1519-29.
12. Pedersen SE, Bateman ED, Bousquet J, Busse WW, Yoxall S, Clark TJ. Determinants of response to fluticasone propionate and salmeterol/fluticasone propionate combination in the gaining optimal asthma control study. *J Allergy Clin Immunol* 2007; **120**: 1036-42.
13. Chaudhuri R, Livingston E, McMahon AD, Thomson L, Borland W, Thomson NC. Cigarette smoking impairs the therapeutic response to oral corticosteroids in chronic asthma. *Am J Respir Crit Care Med* 2003; **168**: 1308-11.
14. Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet* 2006; **368**: 744-753.
15. O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, Ekstrom T, Bateman ED. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005; **171**: 129-136.

16. Papi A, Corradi M, Pigeon-Francisco C, Baronio R, Siergiejko Z, Petruzzelli S, Fabbri LM, Rabe KF. Beclometasone-formoterol as maintenance and reliever treatment in patients with asthma: A double-blind, randomised controlled trial. *Lancet Respir Med* 2013; **1**: 23-31.
17. Patel M, Pilcher J, Pritchard A, Perrin K, Travers J, Shaw D, Holt S, Harwood M, Black P, Weatherall M, Beasley R. Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: A randomised controlled trial. *Lancet Respir Med* 2013; **1**: 32-42.
18. Patel M, Pilcher J, Chan A, Perrin K, Black P, Beasley R. Six-month in vitro validation of a metered-dose inhaler electronic monitoring device: Implications for asthma clinical trial use. *J Allergy Clin Immunol* 2012; **130**: 1420-2.
19. Patel M, Pilcher J, Travers J, Perrin K, Shaw D, Black P, Weatherall M, Beasley R. Use of metered-dose inhaler electronic monitoring in a real-world asthma randomized controlled trial. *J Allergy Clin Immunol Pract* 2013; **1**: 83-91.
20. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, Casale TB, Chanez P, Enright PL, Gibson PG, de Jongste JC, Kerstjens HA, Lazarus SC, Levy ML, O'Byrne PM, Partridge MR, Pavord ID, Sears MR, Sterk PJ, Stoloff SW, Sullivan SD, Szefler SJ, Thomas MD, Wenzel SE. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009; **180**: 59-99.
21. Symbicort SMART Asthma Action Plan. (National Asthma Council Australia). From http://www.nationalasthma.org.au/health-professionals/tools-for-primary-care/asthma-action-plans/asthma-action-plan-library. [Accessed 28 June 2012].

22. Holt S, Masoli M, Beasley R. The use of the self-management plan system of care in adult asthma. *Prim Care Respir J.* 2004; **13**: 19-27.
23. Balanag VM, Yunus F, Yang PC, Jorup C. Efficacy and safety of budesonide/formoterol compared with salbutamol in the treatment of acute asthma. *Pulm Pharmacol Ther* 2006; **19**: 139-47.
24. Rubinfeld AR, Scicchitano R, Hunt A, Thompson PJ, Van Nooten A, Selross O. Formoterol Turbuhaler as reliever medication in patients with acute asthma. *Eur Respir J* 2006; **27**: 735-41.
25. Aaronson D, Kaiser H, Dockhorn R, Findlay S, Korenblat P, Thorsson L, Kallen A. Effects of budesonide by means of the Turbuhaler on the hypothalmic-pituitary-adrenal axis in asthmatic subjects: a dose-response study. *J Allergy Clin Immunol* 1998; **101**: 312-319.
26. van Schayck OC, Haughney J, Aubier M, Selroos O, Ekstrom T, Ostinelli J, Buhl R. Do asthmatic smokers benefit as much as non-smokers on budesonide/formoterol maintenance and reliever therapy? Results of an open label study. *Respir Med* 2012; **106**: 189-196.
27. Ministry of Health. 2010. Tatau Kahukura: Maori Health Chart Book 2010, 2nd Edition. Wellington: Ministry of Health.
28. Pilcher J, Patel M, Smith A, Davies C, Pritchard A, Travers J, Black P, Weatherall M, Beasley R, Harwood M. Combination budesonide/formoterol inhaler as maintenance and reliever therapy in Maori with asthma. *Respirology* 2014; **19**: 842-851.

Table 1. Characteristics of trial participants

	Current Smoker		Ex smoker		Never Smoker	
	Smart	**Standard**	**Smart**	**Standard**	**Smart**	**Standard**
	N=30	**N=29**	**N=49**	**N=48**	**N=72**	**N=75**
Age, years Mean (SD)	39.8 (11.5)	39.0 (12.6)	44.3 (12.7)	45.1 (14.4)	39.9 (14.9)	42.4 (15.2)
Male, no (%)	13 (43.3)	8 (27.6)	10 (20.4)	13 (27.1)	25 (34.7)	25 (33.3)
Duration of asthma, years, mean (SD)	28.8 (12.2)	24.9 (11.9)	30.1 (14.5)	24.3 (14.2)	23.6 (14.8)	27.8 (15.8)
ACQ-7 Score Mean (SD)	2.4 (0.9)	2.8 (1.2)	1.9 (1.1)	1.7 (1.1)	1.6 (0.9)	1.6 (0.9)
ACQ Band, no (%)						
≤ 0.75	1 (3.3)	1 (3.5)	7 (14.3)	9 (18.8)	12 (16.7)	14 (18.7)
0.75 to 1.5	2 (6.7)	2 (6.9)	13 (26.5)	14 (29.2)	19 (26.4)	23 (30.7)
≥1.5	27 (90.0)	26 (89.7)	29 (59.2)	25 (52.1)	41 (56.9)	38 (50.7)
Baseline FEV_1 Mean (SD)	2.72 (1.10)	2.42 (0.67)	2.35 (0.69)	2.50 (0.86)	2.77 (0.92)	2.53 (0.77)
Baseline FEV_1 % predicted, %, Mean (SD)	79.2 (18.1)	76.5 (20.8)	79.3 (20.7)	81.5 (19.3)	84.2 (17.9)	81.2 (21.2)
Severe exacerbation in 12 months before recruitment, no (%)	26 (86.7)	25 (86.2)	46 (93.9)	47 (97.9)	65 (90.3)	69 (92)
ICS dose, mcg of budesonide equivalent, Mean (SD)	819 (411)	808 (320)	820 (309)	839 (372)	788 (359)	797 (391)
LABA use, no (%)	18 (60.0)	19 (65.5)	34 (69.4)	34 (70.8)	40 (55.6)	50 (66.7)
Spacer use, no (%)	14 (46.7)	14 (48.3)	31 (54.4)	26 (54.2)	30 (41.7)	35 (46.7)
Pre-study use of a written asthma self-management plan, no (%)	1 (3.3)	3 (10.4)	10 (20.4)	7 (14.6)	4 (5.6)	10 (13.3)
Māori, no (%)	8 (26.7)	7 (24.1)	11 (22.5)	7 (14.6)	6 (8.3)	5 (6.7)

Pack year history Median (range)	7 (1 to 40)	9 (0.3 to 44)	5 (0.2 to 34)	4 (1 to 60)	0 (0 to 0)	0 (0 to 0)

ICS dose conversion: 500mcg fluticasone = 800mcg budesonide, 1000mcg beclomethasone = 800mcg budesonide.

ACQ: Asthma control questionnaire, FEV_1: forced expiratory volume in 1 second, ICS: inhaled corticosteroid, LABA: long acting beta-agonist, no: number, SD: standard deviation

Table 2. Severe asthma exacerbations, corticosteroid exposure and efficacy outcomes in the SMART and Standard groups and interaction with smoking status

Outcome	Current smoker		Ex smoker		Never smoker		SMART Versus Standard (adjusted for smoking status)	Interaction term fo effect of smoking on response to SMART vs Standard
	SMART N=30	Standard N=29	SMART N=49	Standard N=48	SMART N=72	Standard N=75		
Participants with at least one severe exacerbation, no. (%)	2 (6.7)	8 (27.6)	13 (26.5)	24 (50.0)	13 (18.1)	18 (24.0)	0.45 (0.26 to 0.77)* P= 0.004	0.29
Number of severe exacerbations, weighted mean rate per year (SD)	0.14 (0.55)	0.94 (1.79)	1.02 (2.41)	1.39 (1.58)	0.46 (1.12)	0.67 (1.35)	0.55 (0.37 to 0.81)† P= 0.002	0.11
Participants with at least one hospital admission or ED attendance	0 (0)	2 (6.9)	4 (8.2)	6 (12.5)	3 (4.2)	1 (1.3)	0.76 (0.27 to 2.11)* P=0.59	0.48
Daily budesonide dose, mcg, mean (SD)	1598 (3159)	742 (616)	930 (693)	702 (314)	680 (304)	650 (319)	1.22 (1.06 to 1.41)‡ P= 0.006	0.085
Number of courses of oral corticosteroids per year of follow-up, mean (SD)	0.29 (1.25)	0.94 (1.79)	1.45 (3.88)	1.81 (2.30)	0.57 (1.48)	0.79 (1.55)	0.59 (0.41 to 0.85)† P= 0.004	0.47

Composite systemic corticosteroid exposure, mg prednisone equivalent per year,§ mean (SD)	812 (527)	725 (579)	1047 (1346)	1048 (1715)	617 (535)	611 (470)	1.03 (0.87 to 1.22) ‡ P= 0.76	0.62
FEV1 at final visit, Litres, mean (SD)	2.92 (1.17) (N=24)	2.67 (0.92) (N=29)	2.53 (0.67) (N=41)	2.67 (0.98) (N=45)	2.93 (0.92) (N=68)	2.60 (0.91) (N=67)	0.04 (-0.06 to 0.14) P=0.43	0.63
ACQ 7 Score at final visit, mean (SD)	1.10 (0.73) (N=25)	1.75 (1.40) (N=29)	1.03 (0.90) (N=42)	1.15 (0.92) (N=46)	1.02 (0.70) (N=68)	1.21 (1.0) (N=67)	-0.23(-0.43 to -0.32) P=0.023	0.43

Data summaries are presented as number (percentage) or mean (standard deviation). Odds ratios,* relative rates† and ratio of means‡ are reported with 95% confidence intervals. The weighted mean rate per year is the total number of events in the study group/total person follow-up time in years for the study group. Relative rates were calculated by Poisson regression with an offset of the logarithm of the period of observation (for the analyses of severe exacerbation and number of courses of systemic corticosteroid), unless otherwise stated.

N values are as per column headings unless otherwise stated.

§ Corticosteroid conversion: 100mg intravenous hydrocortisone = 25mg oral prednisone. Budesonide dose was converted to prednisone equivalent dose, based on a bioequivalence conversion calculated in a prior study (5000mcg budesonide=10mg prednisone).[25] The sum of the prednisone equivalent dose and systemic corticosteroid dose was annualised. The logarithm of the annualised steroid use was the response variable in a weighted normal linear model, with the randomised treatment as a predictor and the treatment exposure time as a weight (individuals with longer periods of treatment exposure were given more weight and those with shorter periods of treatment exposure less weight in the analysis).

Abbreviations: no.: number, SD: Standard deviation.

Table 3. Medication use outcomes in the SMART and Standard groups and interaction with smoking status

Outcome	Current smoker		Ex smoker		Never smoker		SMART Versus Standard (adjusted for smoking status)	Interaction term for effect of smoking on response to SMART vs Standard
	SMART (n=30)	Standard (n=29)	SMART (n=49)	Standard (n=48)	SMART (n=72)	Standard (n=75)		
High beta-agonist use								
At least one episode of high beta-agonist use, no. (%)	21 (70.0)	18 (62.1)	34 (69.4)	21 (43.8)	29(40.3)	29 (38.7)	1.56 (0.98 to 2.48)* P= 0.061	0.18
Number of days of high use	9.7 (15.7)	18.7 (34.1)	7.2 (20.8)	8.5 (18.2)	1.7 (3.5)	5.4 (13.5)	0.59 (0.37 to 0.87)† P= 0.007	0.11
Number of days of high use without medical review in participants with at least one high use episode	13.2 (17.2) n=21	28.2 (35.6) n=18	9.6 (23.7) n=34	16.8 (20.4) n=21	3.8 (4.4) n=29	13.2 (17.6) n=29	0.48 (0.31 to 0.74)† P <0.001	0.47
Marked beta-agonist overuse								
At least one episode of marked overuse, no. (%)	16 (53.3)	17 (58.6)	22 (44.9)	18 (37.5)	16(22.2)	21 (28.0)	0.93 (0.58 to 1.52)* P= 0.79	0.53
Number of days of marked overuse	4.4 (7.6)	11.5 (29.0)	4.4 (16.4)	4.6 (9.7)	0.8 (2.3)	2.4 (7.1)	0.57 (0.37 to 0.87)† P= 0.01	0.08

Extreme beta-agonist overuse								
At least one episode of extreme overuse, no. (%)	12 (40.0)	16 (55.2)	17 (34.7)	14 (29.2)	12 (16.7)	10 (13.3)	1.02 (0.60 to 1.74)* P= 0.92	0.37
Number of days of extreme overuse	2.5 (4.4)	8.2 (26.1)	2.6 (10.9)	2.4 (5.2)	0.5 (1.7)	1.1 (4.0)	0.56 (0.35 to 0.90)† P= 0.014	0.055
Underuse of maintenance budesonide/formoterol treatment								
At least one day of zero actuations, no. (%)	23 (76.7)	25 (86.2)	37 (75.5)	44 (91.7)	60 (83.3)	57 (77.0)	0.77 (0.43 to 1.37)* P= 0.37	0.07
Number of days of zero actuations	23.9 (36.8)	57.7 (58.4)	22.8 (32.0)	29.6 (37.7)	24.6 (31.5)	27.2 (35.6)	0.73 (0.56 to 0.96)† P= 0.021	0.12
At least one day of one or less actuation, no. (%)	23 (76.7)	26 (89.7)	40 (81.6)	44 (91.7)	66 (91.7)	62 (83.8)	0.85 (0.44 to 1.64)* P= 0.62	0.06
Number of days with one or less actuations	28.7 (41.4)	59.4 (58.4)	28.0 (35.0)	34.3 (41.2)	29.4 (33.5)	30.2 (38.1)	0.80 (0.62 to 1.03)† P= 0.087	0.18

Data summaries are mean (standard deviation) unless otherwise stated. The weighted mean rate per year is the total number of events in the study group/total person follow-up time in years for the study group.

N values are as per column headings unless otherwise stated.

no.: number.

Odds ratios* and relative rates† are reported with 95% confidence intervals. Relative rates were calculated by Poisson regression with an offset of the logarithm of the period of observation.

Table 4. Severe asthma exacerbations, corticosteroid exposure and efficacy outcomes by smoking status**

Outcome	Smoking status	
	Current vs never	Ex vs never
Participants with at least one severe exacerbation*	0.77 (0.35 to 1.71) P=0.52	2.40 (1.34 to 4.29) P=0.003
Number of severe exacerbations, (weighted mean rate per year)†	0.99 (0.56 to 1.76) P= 0.97	2.03 (1.35 to 3.05) <0.001
Participants with at least one hospital admission or ED attendance*	1.26 (0.22 to 7.08) P=0.79	4.13 (1.26 to 13.6) P=0.02
Daily budesonide dose, mcg‡	1.17 (0.97 to 1.41) P=0.10	1.17 (0.99 to 1.37) P=0.06
Number of courses of oral corticosteroids per year of follow-up†	0.94 (0.54 to 1.65) P=0.84	2.19 (1.49 to 3.22) P <0.001
Composite systemic corticosteroid exposure, mg prednisone equivalent per year§ ‡	1.23 (0.98 to 1.55) P=0.07	1.40 (1.15 to 1.70) P <0.001

Smoking status was significantly associated with all outcome measures above, except daily budesonide dose.

**Adjusted by treatment regimen (SMART vs Standard)

Odds ratios,* relative rates† and ratio of means‡ are reported with 95% confidence intervals. The weighted mean rate per year is the total number of events in the study group/total person follow-up time in years for the study group. Relative rates were calculated by Poisson regression with an offset of the logarithm of the period of observation (for the analyses of severe exacerbation, hospital admission or ED

attendance and number of courses of systemic corticosteroid), unless otherwise stated.

§ Corticosteroid conversion: 100mg intravenous hydrocortisone = 25mg oral prednisone. Budesonide dose was converted to prednisone equivalent dose, based on a bioequivalence conversion calculated in a prior study (5000mcg budesonide=10mg prednisone).[25] The sum of the prednisone equivalent dose and systemic corticosteroid dose was annualised. The logarithm of the annualised steroid use was the response variable in a weighted normal linear model, with the randomised treatment as a predictor and the treatment exposure time as a weight (individuals with longer periods of treatment exposure were given more weight and those with shorter periods of treatment exposure less weight in the analysis).

ED: Emergency Department, mcg: micrograms, no.: number.

Table 5. Medication use outcomes in the SMART and Standard groups by smoking status adjusted by treatment regimen (SMART vs Standard)

	Smoking status	
	Current vs never	**Ex vs never**
High use		
At least one episode of high use, no. (%)*	3.00 (1.59 to 5.68) P <0.001	2.01 (1.19 to 3.40) P=0.009
Number of days of high use†	3.83 (2.36 to 6.22) P <0.001	2.21 (1.35 to 3.62) P=0.002
Number of days of high use without medical review in participants with at least one high use episode†	2.46 (1.47 to 4.13) P<0.001	1.59 (0.92 to 2.72) P=0.088
Marked overuse		
At least one episode of marked overuse, no. (%)*	3.78 (2.00 to 7.13) P <0.001)	2.09 (1.21 to 3.62) P=0.009
Number of days of marked overuse†	4.76 (2.72 to 8.32) P <0.001	2.81 (1.60 to 4.95) P <0.001
Extreme overuse		
At least one episode of extreme overuse, no. (%)*	5.13 (2.59 to 10.2) P <0.001	2.67 (1.43 to 4.97) P=0.002
Number of days of extreme overuse†	6.17 (3.33 to 11.4) P<0.001	2.99 (1.58 to 5.69) P <0.001
Underuse of maintenance budesonide/formoterol		
At least one day of zero actuations, no. (%)*	1.09 (0.50 to 2.35) P=0.83	1.26 (0.64 to 2.47) P=0.50
Number of days of no actuations†	1.53 (1.11 to 2.12) P=0.01	1.02 (0.74 to 1.40) P=0.90
At least one day of one or less actuation, no. (%)*	0.69 (0.44 to 1.64) P=0.39	0.91 (0.42 to 1.96) P=0.81
Number of days with one or less actuations†	1.44 (1.05 to 1.97) P=0.024	1.05 (0.78 to 1.42) P=0.74

Smoking status was not significantly associated with at least one day of zero actuations, at least one day of one or less actuations and number of days with one or less actuations. Smoking status was significantly associated all other outcome measures above.

Odds ratios* and relative rates† are reported with 95% confidence intervals. The weighted mean rate per year is the total number of events in the study group/total person follow-up time in years for the study group. Relative rates were calculated by Poisson regression with an offset of the logarithm of the period of observation.

no.: number.

Figure 1: Flow of participants through the study